

REMARKS

Claims 3, 4, 7, 9-11 and 16-22 are pending in this application. By this Amendment, claims 3, 4, 21 and 22 are amended. Support for the amendments to claims 3, 4, 21 and 22 can be found in the specification as originally filed, for example, at page 19, lines 12-13; and in original claims 3, 4, 21 and 22, and deleted matter is canceled without prejudice to or disclaimer of the deleted subject matter. In addition, the specification is amended herein. Support for the amendments to the specification can be found in the specification as originally filed, for example, at page 12, lines 7-23. No new matter is added by these amendments.

Applicants appreciate the courtesies shown to Applicants' representative by Examiner Le in the July 27, 2005, personal interview. Applicants' separate record of the substance of the interview is incorporated into the following remarks.

I. Objections to the Specification

The Office Action objects to the specification because of typographical errors therein. By this Amendment, the specification is amended to correct typographical errors and to more clearly set forth the terms of art "critical solution temperature" and "lower critical solution temperature," as requested by the Examiner during the July 27 personal interview. Withdrawal of the objection is thus respectfully requested.

II. Claim Rejections Under 35 U.S.C. §112

A. First Paragraph

The Office Action rejects claims 3, 4, 7, 9-11 and 16-22 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. In particular, the Office Action asserts that the terms "reduced pressure" and "lower critical solution temperature" are unclear and that the term "critical solution temperature" is undefined. Applicants respectfully traverse.

Independent claims 3 and 4, including the term "reduced pressure," are clearly enabled by the specification. The term "reduced pressure" is regularly used by those skilled in the art to indicate pressures below atmospheric pressure. Although the specification does not explicitly set forth this understanding or explain a standard or normal pressure relative to "reduced pressure," one of ordinary skill in the art would have readily understood the term "reduced pressure" to mean a pressure lower than atmospheric pressure. However, in the interests of furthering prosecution, claims 3 and 4 have been amended herein to replace the term "reduced pressure" with the phrase --a pressure of 10^{-2} -10 mbar ($1\text{-}10^3$ Pa)--. For at least these reasons, independent claims 3 and 4, and their dependent claims, are fully enabled by the specification.

The term "lower critical solution temperature" in claims 17-20 is also clearly enabled by the specification, and the term "critical solution temperature" is not used in either the specification or the claims. Rather, the term "lower critical solution temperature" is employed to describe a threshold relating to behaviors of grafted polymers. In pores having a low density of grafted polymers, the grafted polymers shrink at temperatures above the lower critical solution temperature, causing the aperture size to increase; the grafted polymers expand at temperatures below the lower critical solution temperature, causing the aperture size to decrease. *See* Specification, page 12, lines 9-15; page 24, line 25 - page 25, line 9; Fig. 8. In pores having a high density of grafted polymers, the grafted polymers become hydrophilic at temperatures below the lower critical solution temperature, allowing migration of inclusions through the graft-filled pores; the grafted polymers become hydrophobic at temperatures above the lower critical solution temperature, blocking migration of inclusions through the graft-filled pores. *See* Specification, page 12, lines 15-21; page 25, line 16 - page 26, line 1; Fig. 9.

Furthermore, these terms are terms of art that are well known and defined in the art. See Perry's Chemical Engineers' Handbook, Sixth Edition, 15-5-15-6 (Don W. Green ed., 1984); Kimura, 3. Development of New pH-Temperature Responsive Polymer, at <http://www.ics.utsunomiya-u.ac.jp/kimura/gel.html>. (copies attached)

Based on the specification and the knowledge of these terms of art, one of ordinary skill in the art would have readily been able to understand the significance of and to identify the lower critical solution temperature for a low- or high-density grafted polymer. One of ordinary skill in the art thus would be able to use the methods of dependent claims 17-20 to prepare functional particles. For at least these reasons, dependent claims 17-20 are fully enabled by the specification.

Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. Second Paragraph

The Office Action rejects claims 3, 4, 7, 9-11 and 16-22 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention.

The Office Action asserts that claims 3 and 4, and their dependent claims, are indefinite because the term "reduced pressure" is unclear. As discussed above, claims 3 and 4 have been amended herein to replace the term "reduced pressure" with the phrase --a pressure of 10^{-2} -10 mbar ($1\cdot 10^3$ Pa)--. For at least the same reasons as discussed above, claims 3, 4 and their dependent claims are not indefinite.

The Office Action also asserts that claim 3 is indefinite because the term "function" in line 16 should be "functional." Claim 3 has been amended to correctly set forth the term "functional" in line 16.

The Office Action asserts that claim 4 is indefinite because it is unclear how a pore that is substantially filled with grafted polymers can be impregnated with an inclusion. However, the step of "impregnating said pore and/or cavity region of said particle with an inclusion" would have been readily understood by one of ordinary skill in the art as providing inclusions into the pore or cavity. In embodiments, this may include soaking the grafted polymers in an inclusion solution that has been adjusted to conditions that shrink, or render hydrophilic, the grafted polymers, allowing penetration of inclusions into the cavity or pore, and changing the conditions of the solution to expand or render hydrophobic the grafted polymers, trapping the inclusions in the cavity or pore. *See* Specification, page 7, lines 5-26. For at least these reasons, the impregnating step of claim 4 would have been clearly understood by one of ordinary skill in the art and is not indefinite.

The Office Action rejects claims 17-20 because the term "lower critical solution temperature" is allegedly unclear. As discussed above, the lower critical solution temperature is a well known term of art. One of ordinary skill in the art would have readily been able to understand the significance of and to identify the lower critical solution temperature for a low or high density grafted polymer. For at least these reasons, dependent claims 17-20 are not indefinite.

The Office Action rejects claims 21 and 22 because it is unclear how the inclusion could be released in response to extent to which the pore is filled with grafted polymers. While Applicants do not necessarily agree with this rejection, claims 21 and 22 are amended herein to clarify the subject matter therein and are not indefinite.

For at least the reasons set forth above, Applicants respectfully submit that claims 3, 4, 7, 9-11 and 16-22 are not indefinite. Reconsideration and withdrawal of the rejections are respectfully requested.

III. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of claims 3, 4, 7, 9-11 and 16-22 are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,



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JAO:JMS/jms

Attachment:

Perry's Chemical Engineers' Handbook, Sixth Edition, 15-5-15-6 (Don W. Green ed., 1984).

Kimura, 3. Development of New pH-Temperature Responsive Polymer, at <http://www.ics.utsunomiya-u.ac.jp/kimura/gel.html>

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PHASE EQUILIBRIUMS

The separation of components by liquid-liquid extraction depends primarily on the thermodynamic equilibrium distribution of those components between the two liquid phases. Knowledge of these distribution relationships is essential for selecting the ratio of extraction solvent to feed that enters an extraction process and for evaluating mass-transfer rates or theoretical stage efficiencies achieved in extraction equipment. Since two liquid phases that are immiscible are involved, the thermodynamic equilibrium involves considerable evaluation of nonideal solutions. In the simplest case a feed solvent F contains a solute that is to be transferred into an extraction solvent S.

DISTRIBUTION COEFFICIENTS

The weight fraction of solute in the extract phase y divided by the weight fraction of solute in the raffinate phase x at equilibrium is called the distribution coefficient, or partition coefficient, K [Eq. (15-1)].

$$K = y/x \quad (15-1)$$

Thermodynamically the distribution coefficient K^* is derived in terms of the weight fractions y^* and x^* [Eq. (15-2)].

$$K^* = y^*/x^* \quad (15-2)$$

In shortcut calculations the distribution coefficient K' in Bancroft coordinates using the weight ratio of solute to extraction solvent in the extract phase Y and the weight ratio of solute to feed solvent in the raffinate phase X is preferred [Eq. (15-3)].

$$K' = Y/X \quad (15-3)$$

In shortcut calculations the slope of the equilibrium line in Bancroft coordinates is also used [Eq. (15-4)].

$$m = dY/dX \quad (15-4)$$

At low concentrations in which the equilibrium line is linear the value of K' is equal to m .

The value of K' is one of the main parameters used to establish the maximum ratio of extraction solvent to feed solvent that can be

employed in an extraction process. For example, if the distribution coefficient K' is 4, then a countercurrent extractor would require 0.25 kg or more of extraction-solvent flow to remove all the solute from 1 kg of feed-solvent flow.

The relative separation, or selectivity, α between two components, b and c , can be described by the ratio of the two distribution coefficients [Eq. (15-5)].

$$\alpha(b/c) = K_b^*/K_c^* = K_b/K_c = K_b'/K_c' \quad (15-5)$$

This is analogous to relative volatility in distillation.

PHASE DIAGRAMS

Ternary-phase equilibrium data can be tabulated as in Tables 15-1 and 15-2 or presented on equilateral-triangular diagrams as shown in Fig. 15-7 *a* and *b*. The water-acetic acid-methyl isobutyl ketone

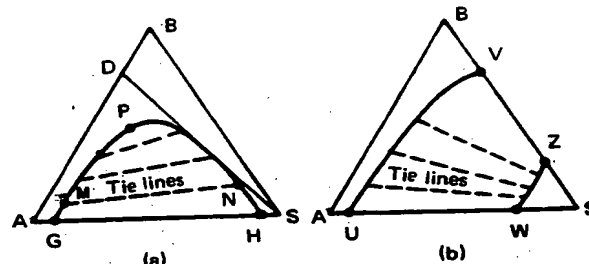


FIG. 15-7 Equilateral-triangular phase diagrams. (a) Type I. (b) Type II. A = feed solvent, B = solute, S = extraction solvent, and P = plait point.

(MIBK) ternary is a Type I system in which only one of the binary pairs is immiscible. The ethyl benzene-styrene-ethylene glycol ternary is a Type II system in which two of the binary pairs are immiscible. The tie lines connect the points that are in equilibrium.

TABLE 15-1 Water-Acetic Acid-Methyl isobutyl Ketone, 25°C*

Weight % in raffinate				Weight % in extract			
Water	Acetic acid	MIBK	X	Water	Acetic acid	MIBK	Y
98.45	0	1.55	0	2.12	0	97.88	0
95.46	2.85	1.7	0.0299	2.80	1.87	95.33	0.0196
85.8	11.7	2.5	0.1364	5.4	8.9	85.7	0.1039
75.7	20.5	3.8	0.2708	9.2	17.3	73.5	0.2354
67.8	26.2	6.0	0.3864	14.5	24.6	60.9	0.4039
55.0	32.8	12.2	0.5964	22.0	30.8	47.2	0.6525
42.9	34.6	22.5	0.8065	31.0	33.6	35.4	0.9492

*From Sherwood, Evans, and Longcor [Ind. Eng. Chem., 31, 599 (1939)].

TABLE 15-2 Ethyl Benzene-Styrene-Ethylene Glycol, 25°C*

Weight % in raffinate				Weight % in extract			
Ethyl benzene	Styrene	Ethylene glycol	X	Ethyl benzene	Styrene	Ethylene glycol	Y
90.56	8.63	0.81	0.0053	9.85	1.64	88.51	0.0185
80.40	18.67	0.93	0.2322	9.31	3.49	87.20	0.0400
70.49	28.51	1.00	0.4045	8.72	5.48	85.80	0.0639
60.93	37.96	1.09	0.6233	8.07	7.45	84.48	0.0882
53.55	45.25	1.20	0.8450	7.35	9.25	83.40	0.1109
52.96	45.84	1.20	0.8656	7.31	9.49	83.20	0.1141
43.29	55.32	1.39	1.2779	6.30	12.00	81.70	0.1469
41.51	57.09	1.40	1.3753	6.06	12.54	81.40	0.1541

*From Boobar et al. [Ind. Eng. Chem., 43, 2922 (1951)].

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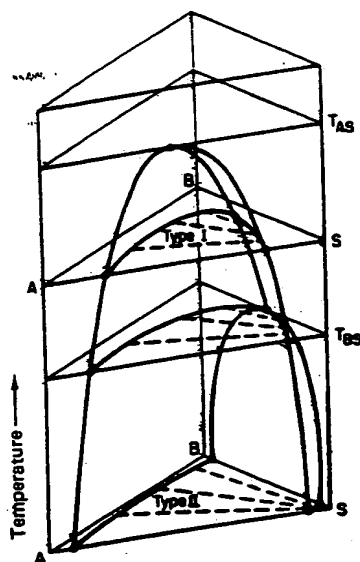


FIG. 15-8 Effect of temperature on ternary liquid-liquid equilibrium. A = feed solvent, B = solute, and S = extraction solvent.

Many immiscible-liquid systems exhibit a critical solution temperature beyond which the system no longer separates into two liquid phases. This is shown in Fig. 15-8, in which an increase in temperature can change a Type II system to a Type I system above the critical temperature of the solute and extraction-solvent binary system T_{AS} . The system becomes totally miscible above the critical temperature of the feed solvent and extraction-solvent binary system T_{AS} . Occasionally a system can also have a lower critical solution temperature

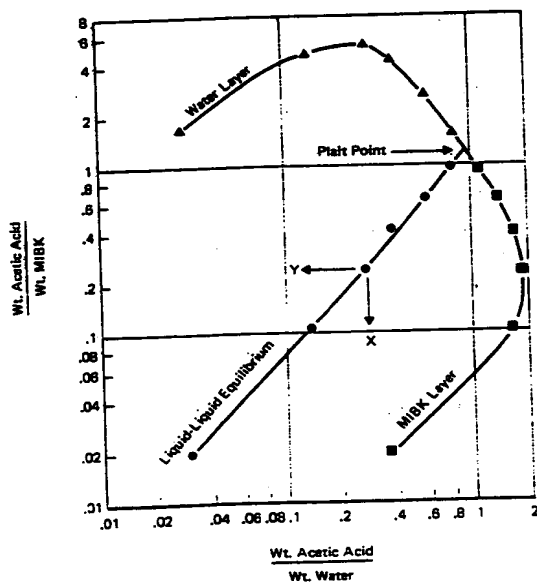


FIG. 15-9 Hand-type ternary diagram for water-acetic acid-methyl isobutyl ketone.

TABLE 15-3 Correlation of Liquid-Liquid Equilibrium Data for Water-Acetic Acid-MIBK System

X	Y (observed)	Y (calculated)
0.0299	0.0196	0.0196
0.1364	0.1039	0.1039
0.2708	0.2354	0.2353
0.3864	0.4039	0.3725
0.5964	0.6525	0.6520
0.8065	0.9492	0.9623

$$\begin{aligned} \text{Exponent} &= \log(0.6525/0.2354) = 1.29 \\ \text{Constant} &= \log(0.5964/0.2708) = 1.27 \\ Y(\text{calculated}) &= 1.27(X)^{1.29}, \text{ for } X \text{ above } 0.25 \\ \text{Exponent} &= \log(0.1039/0.0196) = 1.10 \\ \text{Constant} &= 0.1039/(0.1364)^{1.10} = 0.930 \\ Y(\text{calculated}) &= 0.930(X)^{1.10}, \text{ for } X \text{ between } 0.03 \text{ and } 0.25 \\ Y(\text{calculated}) &= K'X = (0.0196/0.0299)X = 0.656X, \text{ for } X \text{ below } 0.03 \end{aligned}$$

below which the system will be totally miscible. The methyl ethyl ketone-water binary system provides one example. Changes in pressure ordinarily have a negligible effect on liquid-liquid equilibrium.

For graphical calculation of the number of theoretical stages in a ternary system the right-triangular diagram is more convenient to use than an equilateral triangle. The ternary equilibrium data are simply plotted on ordinary rectangular-coordinate-graph paper with the weight fraction of the solute on the horizontal axis and the weight fraction of the extraction solvent on the vertical axis. For low-solute concentrations the horizontal scale can be expanded.

For the McCabe-Thiele type of graphical calculations and shortcut methods, the Bancroft (weight-ratio) concentrations can be used on ordinary rectangular-coordinate-graph paper. The entire ternary system can be plotted in Bancroft (weight-ratio) concentrations on log-log graph paper as shown by Hand [J. Phys. Chem., 34, 1961 (1930)], and the equilibrium line can often be correlated by three straight-line segments (Fig. 15-9 and Table 15-3). The plait-point composition for a Type I system can easily be found by using this Hand plot as shown by Treybal, Weber, and Daley [Ind. Eng. Chem., 38, 817 (1946)]. This type of plot is also helpful for extrapolation and interpolation when data are scarce.

Multicomponent systems containing four or more components become difficult to display graphically. However, process-design calculations can often be made for the extraction of the component with the lowest distribution coefficient K' and treated as a ternary system. The components with higher K' values may be extracted more thoroughly from the raffinate than the solute chosen for design. Or computer calculations can be used to reduce the tedium of multicomponent, multistage calculations.

THERMODYNAMIC BASIS OF LIQUID-LIQUID EQUILIBRIUMS

In a ternary liquid-liquid system, such as the acetic acid-water-MIBK system, all three components are present in both liquid phases. At equilibrium the activity A^* of any component is the same in both phases by definition [Eq. (15-6)].

$$A^*_r = \gamma_r x^* = A^*_e = \gamma_e y^* \quad (15-6)$$

where

$$\begin{aligned} A^* &= \text{activity of solute} \\ \gamma &= \text{activity coefficient of solute} \\ r &= \text{raffinate phase} \\ e &= \text{extract phase} \end{aligned}$$

Consequently, the distribution coefficient in mole-fraction units K' is a result of the ratio of activity coefficients in the two layers [Eq. (15-7)].

$$K' = y^*/x^* = \gamma_r/\gamma_e \quad (15-7)$$

The activity coefficient γ can be defined as the escaping tendency of a component relative to Raoult's law in vapor-liquid equilibrium

(see Sec. 4.1 Design, W. Gmehlin, DEC collection of the resultant liquid equi

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3. Development of New pH-Temperature Responsive Polymer

With the aim of developing a new polymer solution which exhibits a reversible and repetitive transition from a transparent state to an opaque state in response to changes in pH and temperature of external environment and hydrogel which exhibits the transition from an expanded state to a contracted state in response to changes in pH and temperature of external environment, a binary copolymer composed of itaconic acid (a unit that responds to pH) and N-isopropyl acrylamide (a unit that responds to temperature) and a gel of the binary copolymer are prepared. The binary copolymer and a gel thereof are then evaluated with respect to their light transmission behavior and drug release behavior dependent on a phase transition temperature which is also referred to as LCST (lower critical solution temperature).

A phenomenon in which the polymer solution reversibly and repetitively transits from the transparent state to the opaque state in response to changes in temperature is shown in the figure below.

Figure

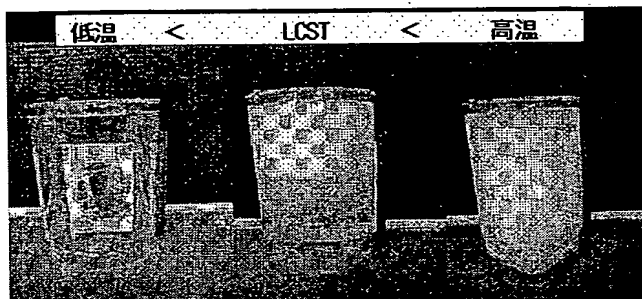
Low Temperature < LCST < High Temperature

There is another effort underway to prepare a latex which exhibits pH/temperature sensitivity with an emulsion copolymerization method for evaluating rheological characteristics thereof.

3. 新奇なpH-温度応答性ポリマーの開発

外部環境のpHと温度に応答して透明-白濁を可逆的に繰り返すポリマー水溶液、また膨潤-収縮を可逆的に繰り返すヒドロゲルの開発を目的として、イタコン酸(pH応答ユニット)とN-イソプロピルアクリルアミド(温度応答ユニット)からなる二元共重合体およびそのゲルを調製し、下限臨界溶液温度(LCST)と呼ばれる相転移温度に依存する光透過挙動、薬物放出挙動を評価している。

下に、相当するポリマー水溶液が温度に応答して可逆的に繰り返す透明-白濁現象を示す。また、乳化共重合法によりpH-温度応答性を示すラテックスを調製し、そのレオロジー特性の評価にも取り組んでいる。



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